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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,598	07/07/2005	Dmitry Antonov	1718-0220PUS1	7502

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EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
04/10/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/526,598	ANTONOV ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/4/2005, 4/21/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This application is a national stage application of PCT/EP03/09872, filed September 5, 2003, which claims priority to foreign application EP02019997.2, filed September 5, 2002.

Claims 1-32 are pending in this application and examined on the merits herein. Applicant's preliminary amendment submitted March 4, 2005 is acknowledged wherein claims 30-32 are amended and the specification is amended to indicate continuity.

Claim Objections

Claim 28 objected to because of the following informalities: The claim is indicated as depending from "any preceding claim." This is not a proper indication of dependence. The correct form is: "as defined in **any of claims 1-27**." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 29 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising 1 to 3 known, art-recognized antiviral drugs such as those recited at the top of p. 9 of the specification, does not reasonably provide enablement for compositions comprising any additional

anti-HIV antiviral drugs whatsoever. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a pharmaceutical composition containing several active ingredients. In order to be enabled for making a composition, one skilled in the art must be able to obtain all of the active ingredients of the composition, typically by purchasing them, isolating them as natural products, or synthesizing them.

The state of the prior art: Many different antiviral agents are known in the prior art for the treatment of HIV infection. However, the prior art does not exhaustively disclose every possible compound which could be used to treat HIV infection. Currently, research continues onto the discovery and development of additional anti-HIV compounds, and there is no method known by which one skilled in the art could

determine the full extent of the class of all possible anti-HIV compounds, as opposed to merely all currently known anti-HIV compounds, or obtain all of such compounds.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: A virus or virus-infected cell is a complex biological system, and there exist multiple methods by which one could kill it or arrest its growth and replication. Furthermore, even considering one particular enzyme, receptor, or biological pathway, there are multiple approaches one could use to disrupt a particular molecular target. Therefore it is not possible to exhaustively determine the full scope of all anti-HIV compounds merely by logical extrapolation from a limited set of existing anti-HIV compounds. One skilled in the art would, in order to determine the full scope of all possible anti-HIV compounds, have to obtain and test a wide range of unrelated compounds for activity, in order to have a representative sample of potential therapeutic agents.

Furthermore, because many compounds are not readily available in the prior art, one skilled in the art would have to make many of these candidate compounds by chemical synthesis. In order to accomplish this, one skilled in the art would have to develop novel chemical syntheses. The art of chemical synthesis is sufficiently unpredictable, and involves sufficient trial and error, that developing a new synthetic method is an undertaking of unpredictable experimentation.

The Breadth of the claims: The claimed invention is very broad, encompassing all possible antiviral agents that could be used for the treatment of HIV.

The amount of direction or guidance presented: Applicant's specification discloses a list of known anti-HIV agents, such as AZT, ddI, ddC, D4T, 3TC, DAPD, and others. The specification does not disclose an exhaustive list of all possible compounds that could be used to treat HIV.

The presence or absence of working examples: No working examples are provided for the treatment of HIV in a living organism.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the discovery of novel compounds. See MPEP 2164.

The quantity of experimentation necessary: One of ordinary skill in the art, in order to practice the claimed invention with the full range of antiviral agents beyond the meager number disclosed in the specification would be required to test potential compounds *in vivo* to determine whether a particular compound is useful as an anti-HIV antiviral agent. According to the 2006 Chemical Abstracts catalog, (Reference included with PTO-892) The Chemical Abstracts Registry contains entries for approximately 26 million compounds, all of which are potentially included in the claimed invention if they happen to have anti-HIV activity. For most compounds, it is unknown whether they are or are not useful as anti-HIV therapeutic agents. Gathering this data for every compound known to man would involve *in vitro* screening of an enormous diversity of chemical compounds for anti-HIV activity, as well as *in vivo* testing of compounds having this activity involving either human or animal subjects to determine therapeutic utility. *In vitro* testing requires that the compounds to be tested be synthesized and

subjected to an appropriate screening method. As described earlier, synthesis of diverse chemical structures requires novel and unpredictable experimentation in order to develop suitable synthetic methods. *In vivo* animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Human tests impose even greater ethical and regulatory burdens, as well as additional difficulty locating subjects. Because of the unpredictability of the art and the lack of comprehensive working examples covering any significant portion of the total number of potential anti-HIV antivirals, these animal experiments would need to be repeated hundreds of times, and involve the maintenance, killing, dissection, and disposal of thousands of experimental animals, to establish the activity or lack thereof of every possible antiviral agent, thus presenting an a burden of undue experimentation to anyone practicing the invention with the full range of antiviral anti-HIV drugs claimed.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the lack of guidance or working examples, Applicants fail to

provide information sufficient to practice the claimed invention for all possible anti-HIV antiviral agents.

Claims 30-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating of HIV infection, does not reasonably provide enablement for a method of prophylaxis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is drawn to a therapeutic method for treatment or prevention of a microbial infection. In the absence of an explicit definition in Applicant's specification, the claims are given their broadest reasonable interpretation. See MPEP 2111. Merriam-Webster's Collegiate Dictionary (reference included with PTO-892) defines "prophylaxis as measures designed to preserve health and **prevent** the spread of disease. This reference also defines "prevent" as meaning,

"to deprive of power or hope of acting or succeeding," or "to keep from happening or existing." This definition is taken as representing the ordinary usage of the term "prophylaxis". In order to deprive something of power or hope of acting or succeeding, the preventative agent must be completely effective. "Prophylaxis" as recited in the instant claims, is interpreted to mean the complete and total blocking of all symptoms of a disorder for an indefinite period of time. Merely slowing the onset of disease or making the disease less likely would still leave it with "power or hope of acting or succeeding," and thus not qualify as prevention.

The state of the prior art: Certain antiviral agents are known to be useful for delaying the course of HIV infection or even in some cases avoiding the onset of infection after exposure. However, this treatment does not qualify as a preventative treatment in the sense described above under the heading "Nature of the invention," as it merely reduces the severity of disease, prolongs survival, and reduces the risk of infection rather than completely avoiding all future occurrence of HIV infection. It is noted that no pharmaceutical preventative method, such as a vaccine, is known for HIV.

More generally, prevention of any disorder in the sense being used herein is not a recognized clinical outcome in the art, as no treatment is perfectly effective.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: Prevention of a disease is not the same as treatment of said disease. In order to prevent a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or a limited number of

treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease. In order to practice a preventative method, one of skill in the art must know the answer to several questions in addition to the effectiveness of the therapy in short-term relief of symptoms, including:

1) What is the duration of a single course of therapy? How often must the therapy be administered to completely suppress the disease?

2) Does the subject develop tolerance to the therapy over time? Does the disease eventually progress to a point where the therapy is unable to completely suppress all symptoms? For example, will a metastatic cancer eventually adapt to overcome treatments directed to preventing it from metastasizing into the bone? Or will a case of osteoporosis or rheumatoid arthritis ultimately progress to a point where symptoms develop regardless of which therapy is administered.

3) What are the long-term effects of the therapy? Does it cause progressive damage to the kidneys, liver, or other organs? Does the active agent accumulate in the subject's tissues? Is the minimum dose necessary to completely prevent the disease safe for long-term administration? Are there any steps that can be taken to reduce side effects?

For this reason, many therapies which are suitable for short-term relief of symptoms are not suitable for lifelong prevention of disease. For example, antibiotics, chemotherapeutics, and antiviral drugs are not normally administered to healthy subjects in order to prevent the development of infection or cancer.

The Breadth of the claims: In the absence of an explicit definition in Applicant's specification, "prophylaxis" and "prevention" as recited in the instant claims, are interpreted to mean the complete and total blocking of all symptoms of a disorder for an indefinite period of time. Any therapy which merely reduces the number or severity of symptoms, or which is effective for a period shorter than the subject's remaining lifespan, is considered to be ineffective at prophylaxis of a disorder.

The amount of direction or guidance presented: The claimed non-nucleoside reverse transcriptase inhibitors are shown to have an inhibitory effect on HIV. However, no guidance is given in the specification suggesting any reason to believe that they can fully prevent all future occurrence of HIV infection.

The presence or absence of working examples: No working examples are provided for the treatment of HIV in a living organism.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the prevention of disease. See MPEP 2164.

The quantity of experimentation necessary: As mentioned above, the short-term usefulness of a therapy for relief of symptoms is no guarantee of its long-term usefulness for prevention of disease. Because no guidance is given for the use of the claimed therapeutic method for the long-term prevention of disease, one skilled in the art wishing to practice the invention would be unable to do so without first gathering information as to the long-term effectiveness of the therapy. In particular, one skilled in

the art, in order to practice the invention for prevention of disease, would need to know whether the preventative effect remains potent over the long term.

In order to answer these questions in the absence of any existing data, one skilled in the art, in order to practice the invention, would undertake long-term animal tests, preferably over a period of years, preferably involving a relatively long-lived experimental animal such as dogs or monkeys, or a human clinical trial. Animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Administering the claimed compounds for a period of years to a suitable subject population is an undue amount of experimentation needed in order to practice the full range of the claimed invention. As prevention in the full sense is an extremely high bar for any clinical outcome, there is no reason to believe that the therapy would be successful, and any actual success would be a surprising and unpredictable result.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the nature of the invention and the unpredictability of the art, Applicants fail to provide

information sufficient to practice the claimed invention for the prophylaxis of HIV infection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-32 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 6610714. (Cited in PTO-892, herein referred to as '714) Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-29 of '714 anticipate the claimed invention. Specifically, claim 1 of '714 recites a structure that contains embodiments that anticipate the structure of instant claim 1. R_2 in claim 1 of '714 is an optionally substituted nitrogen containing heterocycle where the nitrogen is located at

the 2 position. According to column 2 lines 41-62 the specification of '714, the term "optionally substituted" in this context is defined as including a list of substituents including SO_2Aryl, (C=O)Aryl, and phenoxy, all of which fall within the limits of the structure of instant claim 1. Claims 2-29 of '714 recite the same additional dependent limitations as instant claims 2-32. Therefore claims 1-29 of '714 anticipate the claimed invention.

Claims 1-32 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-25 and 30-34 of U.S. Patent No. 6716850. (Cited in PTO-892, herein referred to as '850) Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-25 and 30-34 of '850 anticipate the claimed invention. Specifically, claim 1 of '850 recites a structure that contains embodiments that anticipate the structure of instant claim 1. R_2 in claim 1 of '850 is an optionally substituted nitrogen containing heterocycle where the nitrogen is located at the 2 position. According to column 2 lines 28-51 the specification of '850, the term "optionally substituted" in this context is defined as including a list of substituents including SO_2Aryl, (C=O)Aryl, and phenoxy, all of which fall within the limits of the structure of instant claim 1. Claims 2-25 and 30-34 of '850 recite the same additional dependent limitations as instant claims 2-32. Therefore claims 1-25 and 30-34 of '850 anticipate the claimed invention.

Claims 1-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 and 31-37 of copending Application No. 10/584933. (Published as US publication 2008/0070951, cited in PTO-892, herein referred to as '933) Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-16 and 31-37 of '933 anticipate the claimed invention. Specifically, the compound described in claim 1 of '933 falls within the limits of the structure described in instant claim 1. Claims 2-16 and 31-37 of '933 recite the same additional limitations as the dependent claims 2-32 in the instant application. Therefore claims 1-16 and 31-37 anticipate the claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/
Examiner, Art Unit 1623
3/27/2008

/Shaojia Anna Jiang, Ph.D./
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